

**AMENDMENTS TO THE SPECIFICATION:**

**Please replace paragraph beginning at page 5, line 37, with the following paragraph marked to show changes:**

-- Figure 3 shows a Multiple Sequence Alignment (MSA) of human TNFSF members (SEQ ID NOS:1-17). Amino Acids in the alignment are differentially highlighted according to 6 groupings of physicochemical properties as follows: nonpolar (A, C, I, L, M, V), aromatic (F, W, Y), neutral polar (N, Q, S, T), charged positive (H, K, R), charged Negative (D, E), and conformational (G, P). Figure 3 also shows position numberings of each individual sequence. For TNF- $\alpha$  (TNFA) and TNFB (LT- $\alpha$ ) (SEQ ID NOS:1-2), the numbering is based on current convention. For all other sequences, the numbering is based on the full-length precursor sequence of the protein. For sequences in which a structure of the ligand-receptor complex has been determined experimentally (e.g. TNFB, TRAIL, BLyS), or is readily modeled (e.g. TNFA), position numbers that lie at the ligand-receptor interface are highlighted in gray. Positions highlighted for RANKL have been experimentally determined to affect receptor binding. Receptor interfaces, highlighted in black, are used to define 7 general receptor contact regions of the TNF superfamily ligands. A generic numbering system, beginning with position number 1, is also included above the MSA for reference. --

**Please replace paragraph beginning at page 8, line 1, with the following paragraph marked to show changes:**

-- By "extracellular domain" or "ECD" as used herein is meant the segment of protein existing predominantly outside the cell, generally soluble when cleaved or isolated away from the rest of the protein. For transmembrane proteins, this segment can be tethered to the cell through a transmembrane domain or released from the cell through proteolytic digestion. Alternatively, the extracellular domain could comprise the whole protein or amino acid segments thereof when secreted from the cell. In general, TNFSF members are expressed as type II transmembrane proteins (extracellular C terminus). The unprocessed protein generally contains an atypical signal anchor/intracellular domain of about 10 to 80

amino acids. The extracellular region may be about 140-215 amino acids in length. Soluble forms of TNFSF proteins may result from proteolytic cleavage of the signal propeptide by matrix metalloproteinases termed TNF-alpha converting enzymes (TACE) or directly by recombinant methods. Figure 3 depicts a number of extracellular domains from a number of different TNFSF proteins (SEQ ID NOS:1-17). As will be appreciated by those in the art, these domains may be shorter or longer than those depicted in Figure 3. --

**Please replace paragraph beginning at page 9, line 21, with the following paragraph marked to show changes:**

--Representative amino acid sequences of ~~naturally~~ naturally occurring human TNFSF are shown in Figure 3 (SEQ ID NOS:1-17). It should be noted, that unless otherwise stated, all positional numbering of variant TNFSF proteins and variant TNFSF nucleic acids is based on these sequences. That is, as will be appreciated by those in the art, an alignment of TNFSF proteins and variant TNFSF proteins may be done using standard programs, as is outlined below, with the identification of "equivalent" positions between the two proteins. Thus, the variant TNFSF proteins and nucleic acids of the invention are non-naturally occurring; that is, they do not exist in nature. --

**Please replace paragraph beginning at page 17, line 26, with the following paragraph marked to show changes:**

-- In another embodiment, coiled-coil motifs are used to assist dimer assembly (see Dahiyat et al., Protein Science 6:1333-7 (1997) and U.S.S.N. 09/502,984; both of which are incorporated herein by reference in their entirety). Coiled coil motifs comprise, but is not limited to one of the following sequences:

RMEKLEQKVKELLRKNERLEEEVERLKQLVGER (SEQ ID NO:18), based on the structure of

GCN4; AALESEVSALESEVASLESEVAAL (SEQ ID NO:19), and

LA AVKSKLSAVKSKLASVKSKLAA (SEQ ID NO:20), coiled-coil leucine zipper regions defined previously (see Martin et al., EMBO J. 13(22): 5303-5309 (1994), incorporated by reference). Other

coiled coil sequences from e.g. leucine zipper containing proteins are known in the art and are used in this

invention. See, for example, Myszka et al., Biochem. 33:2362-2373 (1994), hereby incorporated by reference). --

**Please replace paragraph beginning at page 23, line 26, with the following paragraph marked to show changes:**

-- The nucleic acid may be double stranded, single stranded, or contain portions of both double stranded or single stranded sequence. As will be appreciated by those in the art, the depiction of a single strand ("Watson") also defines the sequence of the other strand ("Crick"); ~~thus the sequence depicted in Figure 6 also includes the complement of the sequence.~~ --

**Please replace paragraph beginning at page 34, line 8, with the following paragraph marked to show changes:**

-- Useful linkers include glycine-serine polymers (including, for example, (GS)<sub>n</sub>, (GSGGS)<sub>n</sub> (SEQ ID NO:21), (GGGGS)<sub>n</sub> (SEQ ID NO:22) and (GGGS)<sub>n</sub> (SEQ ID NO:23), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers such as the tether for the shaker potassium channel, and a large variety of other flexible linkers, as will be appreciated by those in the art. Glycine-serine polymers are preferred since both of these amino acids are relatively unstructured, and therefore may be able to serve as a neutral tether between components. Secondly, serine is hydrophilic and therefore able to solubilize what could be a globular glycine chain. Third, similar chains have been shown to be effective in joining subunits of recombinant proteins such as single chain antibodies. --

**Please replace paragraph beginning at page 34, line 16, with the following paragraph marked to show changes:**

-- Suitable linkers may also be identified by screening databases of known three-dimensional structures for naturally occurring motifs that can bridge the gap between two polypeptide chains. Another way of obtaining a suitable linker is by optimizing a simple linker, e.g., (Gly<sub>4</sub>Ser)<sub>n</sub> (SEQ ID NO:22), through random mutagenesis. Alternatively, once a suitable polypeptide linker is defined, additional linker

Serial No.: 10/611,399  
Filing Date: July 1, 2003

polypeptides can be created by application of PDA™ technology to select amino acids that more optimally interact with the domains being linked. Other types of linkers that may be used in the present invention include artificial polypeptide linkers and inteins. In another preferred embodiment, disulfide bonds are designed to link the two receptor monomers at inter-monomer contact sites. In one aspect of this embodiment the two receptors are linked at distances < 5 Angstroms. In addition, the variant TNFSF polypeptides of the invention may be further fused to other proteins, if desired, for example to increase expression or stabilize the protein. --

**Please insert the enclosed 16-page text entitled “SEQUENCE LISTING” into the specification.**